REMARKS

Claims 6, 9, 10, 12-15, 37, 51 and 53 are pending in the subject application. By this amendment, applicants have canceled claim 37. Applicants have also amended claims 51 and 53. Applicants maintain that this amendment does not raise any issue of new matter. Upon entry of this Amendment, claims 6, 9, 10, 12-15, 51, and 53 will be pending and under examination.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 37, 51 and 53 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, but without conceding the correctness of the Examiner's ground of rejection, applicants note that claim 37 has been canceled without disclaimer or prejudice, thereby rendering moot the Examiner's ground of rejection as to this claim. Applicants further note that claim 51 now recites "wherein the thrombotic disorder is deep vein thrombosis" and claim 53 no longer recites "a cardiovascular disorder", thereby obviating the Examiner's ground of rejection as to claims 51 and 53. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these grounds of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 6 and 53 under 35 U.S.C. §102(b) as allegedly anticipated by the abstract of Squadrito et al. Specifically, the Examiner stated that Squadrito et al. disclose a method of treating acute myocardial necrosis, i.e. myocardial infarction, due to an ischemic event by the administration of anti-TNF antibodies.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that the response below to this ground of

rejection is based on the cited Abstract of Squadrito et al. Applicants are obtaining the corresponding publication and will submit a supplemental communication addressing this rejection in view of the disclosure of the Squarito et al. published document.

Applicants' invention as recited in claim 6 is a method of treating a thrombotic disorder in an individual in need thereof comprising administering a therapeutically effective amount of an anti-human tumor necrosis factor alpha monoclonal antibody or antigen-binding fragment thereof to the individual, wherein the thrombotic disorder is selected from the group consisting of: a thromboembolic disorder, an ischemic event, stroke, acute myocardial infarction, deep vein thrombosis and thrombophlebitis.

Squadrito et al. disclose a method of reducing the effects of reperfusion which produces high levels of tumor necrosis factor-alpha by administering hyperimmune serum containing antibodies, i.e. polyclonal antibodies, against murine tumor necrosis factor to rat subjects. In contrast, applicants claimed method provides for the treatment of a thrombotic disorder by administering monoclonal antibodies against human tumor necrosis factor alpha to an individual, i.e. a human subject. Accordingly, applicants maintain that Squarito et al. do not disclose the instant claimed method as recited in amended claim 6. Accordingly, applicants maintain claims 6 and 53 dependent therefrom are novel over Squadrito et al., and respectfully request that the Examiner reconsider and withdrawn this ground of rejection.

Rejections Under 35 U.S.C. §103

1. Streiter et al.

The Examiner rejected claim 6 under 35 U.S.C. §103(a) as allegedly unpatentable over the abstract of Streiter et al. Specifically, the Examiner stated that it would have been obvious to treat an ischemic event by the administration of anti-TNF antibodies because Streiter et al. disclose the administration of anti-TNF antibodies to reduce organ damage and mortality in ischemic-reperfusion injury.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that the response below to this ground of rejection is based on the cited Abstract of Streiter et al. Applicants are obtaining the corresponding publication and will submit a supplemental communication addressing this rejection in view of the disclosure of the Streiter et al. published document.

Applicants' invention as recited in claim 6 is a method of treating a thrombotic disorder in an individual in need thereof comprising administering a therapeutically effective amount of an anti-human tumor necrosis factor alpha monoclonal antibody or antigen-binding fragment thereof to the individual, wherein the thrombotic disorder is selected from the group consisting of: a thromboembolic disorder, an ischemic event, stroke, acute myocardial infarction, deep vein thrombosis and thrombophlebitis.

The Abstract of Streiter et al. only discloses that a "review of animal and human data defining the role of tumor necrosis factor (TNF) in the pathogenesis of the septic shock syndrome, the systematic inflammatory response syndrome, and related pathologies" was conducted. The data used to assess the state of the art as it relates to the role of TNF was based on data relevant to the pathogenesis of the human systemic inflammatory response syndrome secondary to infection. In contrast, applicants claimed method provides for the treatment of a thrombotic disorder by administering monoclonal antibodies against human tumor necrosis factor alpha to an individual. Applicants maintain that the claimed method is not intended for use secondary to infection. In addition, the Abstract of Streiter et al. does not disclose the administration of a monoclonal antibody against human TNF-alpha. Accordingly, applicants maintain that the Abstract of Streiter et al. do not disclose the instant claimed method as recited in amended claim 6.

Applicants further maintain that that the cited abstract of Streiter et al. is not a proper reference under 35 U.S.C. §102 as it does not

provide an enabling disclosure and thus cannot be cited to reject claim 6 under 35 U.S.C. §103.

According to M.P.E.P. §2121.01, " '[i]n determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'… .' *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003)". As stated in M.P.E.P. §2121.01, possession as of the date of the reference is required for the disclosure to be enabling. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

Applicants maintain that the Abstract of Streiter et al. do not disclose or suggest that the administration of anti-TNF antibodies will *positively* affect, i.e. treat, a subject suffering from a thrombotic disorder or provide any guidance regarding the amount to be administered effective to achieve treatment of such thrombotic disorder. Applicants further maintain that the language in Streiter et al. is speculative and shows that the state of the prior art at the time of publication of Streiter et al. was such that one skilled in the art did not have the knowledge to combine with the sparse disclosure of Streiter et al. to envision and use applicants' claimed method. As of January 17, 2004, one skilled in the art would not have had sufficient knowledge to be able to use applicant's claimed invention without undue experimentation. In fact, applicants maintain that clinical trials conducted after the publication of Streiter et al. demonstrate that the administration of anti-TNF antibodies is not effective in treating septic shock. Applicants attach hereto as Exhibit A a copy of Freeman

and Natanson (1995) which disclose the result of six clinical trials for treatment of septic shock wherein none of the therapeutic strategies improved the survival of the trial subjects. Accordingly, applicants maintain that the Abstract of Streiter et al. could not have been an enabling disclosure as it provides incorrect information. Therefore, applicants maintain that it does not qualify as prior art under 35 U.S.C. §102, and thus is not a proper reference to be cited in the Examiner's rejection under 35 U.S.C. §103.

In view of the remarks above, applicants maintain that the Abstract of Streiter et al. does not disclose applicants' claimed method and further that the rejection of claim 6 as obvious over the Abstract of Streiter et al. is not proper as the Abstract of Streiter et al. does not provide an enabling disclosure. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection

2. Le et al. in view of Bender et al.

The Examiner also rejected claims 6, 9, 10-15, 37, and 53 under 35 U.S.C. §103(a) as allegedly unpatentable over Le et al. (U.S. 5,656,272) in view of Bender et al. (U.S. 5,317,019). Specifically, the Examiner stated that it would have been obvious to substitute myocardial infarction or stroke for the TNF-alpha mediated disease as taught by Le et al. because Bender et al. identify a myocardial infarction and a stroke as TNF-alpha mediated diseases.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that claim 37 has been canceled thereby rendering moot the Examiner's ground of rejection as to this claims.

Applicants' invention as recited in claim 6 is a method of treating a thrombotic disorder in an individual in need thereof comprising administering a therapeutically effective amount of an anti-human tumor necrosis factor alpha monoclonal antibody or antigen-binding fragment thereof to the individual, wherein the thrombotic disorder is selected from the group consisting of: a thromboembolic disorder, an ischemic event, stroke, acute myocardial infarction, deep vein thrombosis and

thrombophlebitis.

Le et al. disclose the administration of anti-TNF antibodies for the treatment of TNF-related pathologies. Le et al. at column 34 enumerate in an exhaustive list the TNF-related pathologies which may be treated by the administration of such antibodies. However, this list does not include any of the thrombotic disorders listed in applicants' claim 6.

Bender et al. disclose a method of inhibiting the production of TNF by monocytes or macrophages by administering specific compounds of Formula (I) or (II) as disclosed in Bender et al.

Applicants maintain that the method of Bender et al. is unlike that of Le et al. as it necessarily does not treat any disorder but inhibits the production of TNF. Applicants maintain that inhibiting production of TNF alpha does not involve the binding of TNF receptor as do anti-TNF antibodies. Applicants therefore maintain that one skilled in the art would not have combined these references as these methods are geared to different results at different stages of TNF production. Accordingly, one skilled in the art could not have assumed that the inhibition of production of TNF would yield the same results as the administration of anti-TNF antibodies to bind with already-produced TNF.

Accordingly, applicants maintain that Le et al. in combination with Bender et al. do not render obvious the instant claimed method, and respectfully request that the Examiner reconsider and withdraw this ground of invention.

2. Le et al. in view of Bender et al. and Naughton et al.

The Examiner also rejected claims 6, 9, 10-15, 37, and 53 under 35 U.S.C. §103(a) as allegedly unpatentable over Le et al. (U.S. 5,656,272) in view of Bender et al. (U.S. 5,317,019) and Naughton et al. . Specifically, the Examiner stated that it would have been obvious to substitute myocardial infraction or stroke for the TNF-alpha mediated disease as taught by Naughton et al. because Naugthon et al.

disclose that thromboembolism is a TNF-mediated disease and that the administration of anti-TNF antibodies can prevent thromboembolism.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that claim 37 has been canceled thereby rendering moot the Examiner's ground of rejection as to this claim.

Applicants' invention as recited in claim 6 is a method of treating a thrombotic disorder in a subject in need thereof comprising administering a therapeutically effective amount of an anti-tumor necrosis factor antibody or antigen-binding fragment thereof to the subject, wherein the thrombotic disorder is selected from the group consisting of: a thromboembolic disorder, an ischemic event, stroke, acute myocardial infarction, deep vein thrombosis and thrombophlebitis.

Le et al. disclose the administration of anti-TNF antibodies for the treatment of TNF-related pathologies. Le et al. at column 34 enumerate in an exhaustive list the TNF-related pathologies which may be treated by the administration of such antibodies. This list does not include any of the thrombotic disorders listed in applicants' claim 6.

Bender et al. disclose a method of inhibiting the production of TNF by monocytes or macrophages by administering specific compounds of Formula (I) or (II) as disclosed in Bender et al. Bender et al. state that TNF is a likely mediator of tissue injury in myocardial infarction and stroke.

Naughton et al. disclose a stromal-cell based three-dimensional system which is in no way related to either the Le et al. or Bender et al. cited references. Naughton et al. do not disclose any method of treating any disorder related to TNF or of preventing the production of TNF. In fact, Naughton et al. only disclose that the stromal-cell based system can be used to engineer peptides corresponding to neutralizing antibodies for TNF.

As stated above, applicants maintain that the method of Bender et al.

is unlike that of Le et al. as it necessarily does not treat any disorder but inhibits the production of TNF. Accordingly, one skilled in the art would not have combined these references as these methods are geared to different results at different stages of TNF production. In addition, applicants maintain that one skilled in the art would not have combined Naughton et al. with either Le et al. or Bender et al. since the subject matter disclosed in Naughton et al. is unrelated. Accordingly, applicants maintain that Le et al. in combination with Bender et al. and Naughton et al. do not render obvious the instant claimed method, and respectfully request that the Examiner reconsider and withdraw this ground of invention.

Conclusion

Applicants respectfully submit that the grounds of rejection set forth in the July 16, 2007 Office Action have now been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw the grounds of rejection, and respectfully request allowance of all claims pending in the subject application, namely claims 6, 9, 10, 12-15, 51, 53 and 54.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $1,050.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

1/16/08

John P. White Date
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Clinical trials in sepsis and septic shock in 1994 and 1995.

Bradley D. Freeman, MD and Charles Natanson, MD

Charles Natanson, MD, Senior Investigator, Critical Care Medicine Department, National Institutes of Health, Building 10, Room 7D43, Bethesda, MD 20892, USA.

Sepsis continues to be a leading cause of death in noncoronary ICUs. In an effort to develop new treatments, researchers have posited several important theories about the sepsis syndrome, including the idea that an oxygen debt causes organ injury, that endotoxin is a critical mediator, and that the host inflammatory response is harmful. These three concepts have been the driving force behind sepsis-related research and drug development for the past decade. However, during 1994 and 1995, results from six clinical trials were published demonstrating that the use of dobutamine to augment oxygen delivery, the use of core lipid A-directed antibodies to bind endotoxin, and the use of anticytokine agents to block inflammation all failed to improve outcome for patients with sepsis or septic shock. At least two of the experimental agents tested actually caused harm. The importance of these negative results should not be underestimated. Widely held assumptions about the pathophysiology of sepsis have been proven either too simplistic or incorrect. Further, this experience confirms that strict adherence to scientific method and appropriate regulatory oversight are needed both to determine whether or not new treatments are effective and to protect patients from potentially harmful interventions.

Current Opinion in Critical Care 1995, 1:349-357

Introduction

In the past year (1994 to 1995), the results of six **clinical** trials were published in which three widely held hypotheses about the pathophysiology and treatment of **septic shock** were tested [1][2][3][4][5][6]. Unfortunately, none of the therapeutic strategies used in these trials improved survival in **septic** patients, and two experimental agents actually increased mortality [1][2][7][8]. One of these studies examined the theory that organ injury in critically ill and **septic** patients is due to inadequate oxygen delivery and that, therefore, increasing oxygen delivery to supernormal levels with beta -adrenergic agents, such as dobutamine, would reverse organ injury and improve outcome [1]. Two **clinical** trials examined the assumption that endotoxin is a critical mediator of sepsis syndrome. Starting from the premise that circulating endotoxin is a viable therapeutic target, the studies were designed to determine whether or not antibodies directed at common epitopes on endotoxin molecules could broadly protect against diverse gram-negative infections (*ie*, the %ccross-protection%c hypothesis) [2][6][9]. Three other **clinical** trials tested the concept that the host inflammatory response to bacteria and bacterial products during sepsis and **septic shock** is harmful. Using experimental agents that specifically inhibit inflammatory mediators, *eg*, anti-tumor necrosis factor- alpha (TNF- alpha) monoclonal antibody, recombinant human interleukin-1 receptor antagonist (rhIL-1ra), and platelet-activating factor (PAF) antagonist, these studies attempted to block or modulate inflammation as a protective measure [3][4][5]. This manuscript reviews these six **clinical** trials and their impact on current hypotheses concerning the treatment of sepsis and **septic shock**.

Augmenting oxygen delivery

Early studies in critically ill patients and animal models of sepsis suggested that oxygen supply may limit oxygen consumption [10][11][12][13][14][15]. Further, in critically ill patients, higher levels of oxygen delivery were associated with improved outcome [16]. An oxygen debt was postulated to contribute to morbidity and mortality in critically ill patients, and **clinical** trials were initiated with the idea of increasing oxygen delivery to supernormal levels in order to improve organ perfusion and outcome [17][18]. More recent studies, however, suggested that the apparent dependency of oxygen delivery on consumption was an artifact of flawed methodologies and misinterpretation of data [19][20][21][22]. A recent study published in June 1994 by Hayes *et al.* [1] casts further doubt on the validity of this approach.

Hayes *et al.* [1] examined the effect of elevating oxygen delivery to supernormal levels with dobutamine in critically ill and **septic** patients in a prospective, randomized, controlled **clinical trial**. Following ICU admission, 109 consecutive patients received intravenous fluid resuscitation adequate to optimize left atrial filling pressures. If after fluid resuscitation patients did not meet three predefined hemodynamic end points associated with improved survival in high-risk patients, *ie*, cardiac index greater than 4.5 L/m^2, oxygen delivery index greater than 600 mL/m^2/min, and oxygen consumption index greater than 170 mL/m^2/min, they were randomly assigned to receive either dobutamine therapy to achieve these targets or to standard care (control group). Nine patients responded to intravenous fluid therapy alone, whereas 100 patients did not and were assigned to one of the two treatment arms. Dobutamine therapy was given in high doses (means, 25 mu g/kg/min; range, 2.5 to 200 mu g/kg/min) and was associated with significant increases in cardiac index and oxygen delivery index. However, this did not result in an increase in oxygen consumption index, suggesting that a global oxygen debt was not present in these patients. Further, dose escalation was limited by complications in 24 patients in the dobutamine group (tachycardia, myocardial ischemia, hypertension, arrhythmias) and requirement for norepinephrine was significantly greater than in control patients. Of concern, this study reported an in-hospital mortality that was significantly higher in patients receiving dobutamine therapy (54% vs 34% for control patients, $P = 0.04$).

In contrast to the above findings, other investigators have reported that augmenting oxygen delivery in critically ill patients was associated with improved outcome. Shoemaker *et al.* [17] previously reported a series of 58 high-risk general surgery patients in whom preoperative augmentation of oxygen delivery using crystalloids, blood products, and vasoactive drugs (principally dobutamine) significantly decreased mortality by 29% as compared with control therapy. Similarly, Boyd *et al.* [23], using dopexamine instead of dobutamine to augment preoperative supraphysiologic oxygen delivery, achieved

a 75% reduction in mortality as compared with control treatment. Tuchsmidt *et al.* [18] showed a 22% reduction in mortality in **septic shock** patients by increasing oxygen delivery to supernormal levels with fluids, blood products, and dobutamine; however, this difference did not reach statistical significance.

Clearly, the adverse effect of inotropic therapy in the study by Hayes *et al.* [1] contradicts the favorable findings reported by Boyd *et al.* [23] and Shoemaker *et al.* [17]. Several possibilities may explain these conflicting results. Two thirds of the patients in Shoemaker *et al's.* study responded to fluids alone whereas in Hayes *et al's.* study, such patients were excluded from the survival analysis. In general, prognosis is favorable for critically ill patients in whom cardiac index, oxygen delivery index, and oxygen consumption index reach target levels with fluids alone, suggesting that these patients possess an adequate physiologic reserve. However, patients who do not respond to fluids appear to have poor physiologic reserve, and the use of aggressive inotropic therapy may be associated with untoward effects (maldistribution of blood flow, myocardial ischemia, dysrhythmias, and so forth) [1][17]. The favorable outcome reported by Boyd *et al.* may be partially attributed to the inclusion of less seriously ill patients (median Acute Physiology and Chronic Health Evaluation II scores of 8 for patients in the study by Boyd *et al.* vs 18 for patients in the study by Hayes *et al.*) and to lower levels of oxygen delivery during treatment periods relative to patients in the study by Hayes *et al.* Sicker patients receiving higher doses of vasoactive drugs may be more susceptible to the untoward effects of vasopressor therapy. Finally, the patients in both Boyd *et al's.* and Shoemaker *et al's.* studies had therapy instituted preoperatively, whereas Hayes *et al.* instituted treatment after ICU admission and frequently after complications had occurred. Possibly, supraphysiologic oxygen delivery may only be beneficial on a prophylactic basis in high-risk surgical patients.

Although it is difficult to fully reconcile the disparate findings in these studies, the data by Hayes *et al.* [1] do suggest that there is no therapeutic benefit in boosting oxygen delivery to an artificially high level with dobutamine in volume-resuscitated, critically ill patients with well-maintained perfusion and adequate mean arterial pressure, nor in volume-resuscitated patients with **septic shock** on vasopressors with adequate perfusion. Further, this study does not support the hypothesis that organ injury and poor outcome in sepsis are due to an oxygen debt requiring supernormal oxygen delivery.

Antiendotoxin therapies in septic shock

In 1994 and 1995, results from two large phase III **clinical** trials testing two different antiendotoxin antibodies were published. Notably, both trials represented the second time that each of these agents were administered to a large number of patients in a randomized, double-blind placebo-controlled design [2][6] (Table 1). E5 (XOMA Corp., Berkeley, CA) and HA-1A (Centoxin, Centocor, Malvern, PA) both failed to improve outcome for **septic** patients and neither therapy has yet been licensed for use in the United States. In fact, the second HA-1A **trial** was terminated prematurely due to excess mortality in the group of HA-1A-treated patients without gram-negative bacteremia [2][7][8][9]. In light of these disappointing results, it is important to consider the rationale behind antiendotoxin therapy.

Circulating endotoxin as a therapeutic target

Gram-negative bacteria are a common cause of **septic shock**, causing 40% to 50% of cases [9]. Endotoxin, a lipopolysaccharide common to the outer membrane of most of gram-negative bacteria, is believed by some to be a central mediator of this syndrome [24] [25][26]. The rationale underlying the use of antibodies directed against endotoxin as a therapy in sepsis assumes that patients with **septic shock** invariably develop endotoxemia; that the degree of endotoxemia correlates with the severity of illness and, thus, lowering the levels of circulating endotoxin will improve outcome; and that endotoxin from heterologous gram-negative bacteria share common binding sites (epitopes) which, when bound to antibody, will result in neutralization or increased clearance and thus improved outcome [9]. Notably, there are several potential flaws in these assumptions. In multiple **clinical** studies of patients with **septic shock**, measurable endotoxemia (picogram quantities) was present only intermittently, and in less than 50% of patients. Further, endotoxemia correlated poorly with culture results, type of infection, and outcome [27] [28]. In addition, experimental data indicate that induced tolerance or decreased sensitivity to endotoxin is not beneficial [29][30]. In fact, mice genetically tolerant to endotoxin are actually more susceptible to gram-negative bacterial infection, suggesting a potentially beneficial role for endotoxin in host defense [31] . Thus, it is unclear whether endotoxin is an essential mediator of the sepsis syndrome and if neutralizing it will improve outcome.

The cross-protection hypothesis

Lipid A, a component of endotoxin that is structurally conserved across different species of gram-negative bacteria, appears to mediate the toxicity of this molecule. Most antiendotoxin antibodies have targeted lipid A to confer %ccross-protection%c against clinically significant gram-negative bacteria [9] . However, lipid A is deeply embedded in the bacterial outer membrane. Consequently, it is unknown whether this molecule is physically exposed and available for antibody binding [9][32][33]. Further, the potential mechanisms of action of these lipid A-directed antiendotoxin antibodies *in vivo*, if any, remain unknown [7][9] [33].

Clinical trials of antiendotoxin cross-protective antibodies

Polyclonal antibodies

The first human **clinical trial** of cross-protective antibodies studied patients with gram-negative sepsis treated with J5 antiserum [34] (Table 1). This antiserum was obtained by immunizing healthy volunteers with the heat-killed J5 mutant of *Escherichia coli* in an attempt to develop antibodies against core structures, *ie*, lipid A, and J5 *E. coli* endotoxin. Overall mortality rates in patients with gram-negative bacteremia who received J5 decreased (39% in the control group vs 22% in the J5 group; $P = 0.01$). However, five subsequent **clinical** trials evaluating polyclonal core-reactive antisera or immunoglobulin have not confirmed these results [35][36][37][38][39] (Table 1).

Monoclonal antibodies

With the advent of hybridoma technology in the late 1970s, monoclonal antibodies against lipid A were developed with the intent of finding more specific cross-protective antibodies than that of polyclonal serum. To date, most **clinical** data has been derived from two such IgM class antibodies: E5 and HA-1A.

Negative trials of E5 and HA-1A

Two large, multicenter, phase III **clinical** trials of E5 in sepsis and **septic shock** have been conducted [6][40] . The first of these trials was unable to demonstrate an overall treatment effect with E5 but suggested a benefit in a retrospectively identified subgroup of patients with nonrefractory **shock** [40]. A second **trial** published in May 1995 enrolled 847 patients with suspected gram-negative sepsis, of which 530 patients were in nonrefractory **shock** [6] . In the treatment group, two doses of E5 (2 mg/kg/d) resulted in an increase in mortality (26% in the placebo group vs 30% in the E5 group; $P = 0.21$). A

retrospective analysis of this study suggested that E5-treated patients with organ failure and gram-negative sepsis had more rapid resolution of organ injury. A third clinical trial is now being conducted to substantiate this finding.

Interpreting published results of the first phase III clinical trial of HA-1A in gram-negative sepsis is difficult due to methodologic flaws [7] [8] [9] [41] [42]. In July 1994, Centocor [2] reported the results of its second phase III trial of HA-1A. After the enrollment of 2199 patients, this randomized, double-blind, placebo-controlled trial was prematurely terminated due to excess mortality in HA-1A-treated patients without gram-negative bacteremia (37% in the placebo group vs 41% in the HA-1A group; $P = 0.073$, Fisher exact one-tailed test). Further, in patients with confirmed gram-negative bacteremia, HA-1A had no beneficial effect on mortality (32% in the placebo group vs 33% in the HA-1A group). The reported increase in mortality in patients without gram-negative infection was consistent with data from both the first clinical trial of HA-1A and the French National Registry, which reported on the outcome of 600 septic patients treated with HA-1A [43] [44] (Table 2). Unfortunately, a substantial number of patients with septic shock may have received this potentially harmful drug.

Summary

In a total of 10 clinical trials, cross-protective antibodies have failed to show consistent benefit (Table 1). It is unclear if this disappointing result is due to the fact that agents lacking the required bioactivity were tested or because endotoxin is not a useful therapeutic target in septic shock. Newer, potentially more potent antiendotoxin agents are currently under study: peptides, lipoproteins (*eg*, high-density lipoprotein, bactericidal permeability-increasing protein), and lipid A derivatives (*eg*, E5531, lipid X). Testing of these agents may finally determine whether endotoxin is a useful therapeutic target in sepsis.

Anti-inflammatory therapies

In 1994 and 1995, three separate anti-inflammatory agents, anti-TNF- alpha monoclonal antibody, rhIL-1ra, and PAF inhibitor, were reported not to improve outcome in patients with septic shock [3] [4] [5] (Table 3). The concept that inhibiting inflammation could improve outcome in sepsis is not new. Corticosteroids were used as adjunctive therapy to treat septic shock more than 20 years ago. The discovery of inhibitors of specific inflammatory mediators (*eg*, interleukin-1, TNF- alpha , PAF, and so forth) renewed interest in this approach. Unfortunately, like corticosteroids, these more specific agents do not appear to improve outcome. Thus, the feasibility of this therapy remains unproven.

High-dose corticosteroids

In the late 1980s, two reports were published that demonstrated that corticosteroids were not beneficial, and were potentially harmful, in patients with septic shock. In one study, methylprednisolone (Medrol, Upjohn Co., Kalamazoo, MI), 75 mg/kg, had no effect on survival (14-day mortality; 22% in the placebo group vs 21% in the group treated with methylprednisolone; $P = 0.97$), and in a second study, high doses of methylprednisolone (120 mg/kg) were associated with increased lethality and did not prevent or reverse shock (14-day mortality, 25% for the placebo group vs 34% for the methylprednisolone group; P less than 0.06) [45] [46] .

Recombinant human interleukin-1 receptor antagonist

Two large, phase III clinical trials of rhIL-1ra (Antril, Synergen, Boulder, CO), a recombinantly produced protein that binds to interleukin-1 receptors and blocks interleukin-1-mediated events, have been conducted in humans with sepsis [4] [7] (Table 3). The first phase III clinical trials of rhIL-1ra failed to confirm an overall beneficial survival effect reported in an open-label phase II study but suggested a benefit in a subgroup of patients with a high predicted risk of mortality [4] [7] [47]. Notably, in June 1994, a second phase III trial failed to confirm a treatment benefit in this retrospectively identified subgroup of patients, and this trial was prematurely terminated due to lack of drug efficacy [48]. This therapy is no longer under investigation for the treatment of septic shock, and Synergen, the developer of rhIL-1ra, has been acquired by Amgen (Thousand Oaks, CA).

Platelet-activating factor antagonists

There have been two large multicenter clinical trials of BN 52021 (Ginkolide B, H. Beaufur, Paris, France), a naturally occurring PAF antagonist, in patients with septic shock (Table 3). The first phase III trial was published in November 1994 [5], whereas data from the second phase III trial is available only in abstract form [49]. Although BN 52021 did not affect overall 28-day mortality in the initial phase III study, it appeared to improve survival in a subgroup of patients with gram-negative infection [5]. The subsequent trial failed to confirm this treatment benefit [49].

Anti-tumor necrosis factor- alpha therapies

Anti-TNF- alpha antibodies failed to show benefit in septic patients in two separate phase II (CB006, CellTech, Slough, UK; and MAK-195F, Knoll AG, Ludwigshafen, Germany) clinical trials [50] (Reinhart *et al.*, Paper presented at the Fifth Vienna Shock Forum, Vienna, 1995) (Table 3). In March 1995, the results of a phase III clinical trial conducted in North America showed that 971 patients infused with placebo or anti-TNF- alpha antibody (Bay-x-1351, Bayer AG, subsidiary of Miles, Biological Products, Berkeley, CA) showed no beneficial effect [3]. A second phase III clinical trial conducted in Europe testing this same anti-TNF- alpha antibody also showed no significant beneficial effect (Carlet *et al.*, Paper presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, 1994). Two additional phase III clinical trials are now being conducted, one by Bayer-Miles, to prospectively test whether anti-TNF- alpha antibody improves outcome in patients with shock, a subgroup retrospectively identified in the first phase III trial. Another phase III trial is being conducted by Knoll, to test whether anti-TNF- alpha antibodies improve outcome in patients with high interleukin-6 levels and shock, a subgroup retrospectively identified during a phase II study.

Another anti-TNF- alpha therapy produced more disturbing results. In patients with sepsis, recombinant human dimeric TNF- alpha p80 receptor (Immunex Corp., Seattle, WA) when administered in low doses, did not alter survival, and when administered in medium or high doses, significantly increased mortality rate [7] (Sadoff *et al.*, Paper presented at the Third International Congress of the Immune Consequences of Trauma, Shock, and Sepsis: Mechanisms and Therapeutic Approaches, Munich, 1995). This result suggests a harmful effect of soluble TNF- alpha receptors in patients with septic shock. Hoffman-LaRoche (Nutley, NJ) is presently investigating a different molecular weight TNF- alpha receptor (p55) for the treatment of patients with septic shock [51].

Summary

The use of anti-inflammatory agents as therapy in patients with sepsis assumes that inflammation in this setting is harmful. However, in 11 clinical trials,

four different types of anti-inflammatory agents studied in 20 different dosages produced either no benefit or harm (Table 3). This result suggests that either the anti-inflammation therapies, as studied, lacked the required bioactivity, or that inhibiting inflammation is not protective in **septic shock**. Inhibiting the host inflammatory response may not be beneficial because the immune response and cytokines play both pathogenic and protective roles [7][8]. It may be difficult to selectively block the harmful effects of proinflammatory mediators while simultaneously maintaining their ability to play a necessary role in host defense (Figure 1). These 11 **clinical** trials testing the anti-inflammation hypothesis raise questions regarding the methodology used, the validity of the approach, or both.

Conclusions

The importance of these six recently published phase III **clinical** trials should not be underestimated [1][2][3][4][5][6]. Three important theories concerning the pathophysiology of sepsis syndrome have been proven either too simplistic or incorrect. In addition, potentially harmful therapies, such as HA-1A and high-dose dobutamine in volume-resuscitated critically ill patients, have been removed from **clinical** use [1][2][7][8][9]. Importantly, four of these six published reports represent one of a series of two phase III **clinical** trials in which therapeutic hypotheses generated from retrospectively identified subgroups were subjected to confirmatory testing [2][4][5][6]. That testing revealed that these retrospective hypotheses were wrong and that the agents studied not only lacked efficacy but in some cases caused harm [7][8][9]. One recent criticism of the current drug development and approval process is that the Food and Drug Administration's strict standards for proof of safety and efficacy may prevent promising new agents from reaching the marketplace in a timely fashion. It has been suggested, for example, that the approval standard, especially for %cimportant new drugs,%c should be more flexible and should rely more heavily on postmarketing surveillance [52]. However, experience with new therapies in sepsis demonstrates that controlled **clinical** trials, strict adherence to scientific method, and a rigorous regulatory process prevented unproven and harmful agents from achieving wide **clinical** application. These six studies illustrate that well-designed **clinical** trials are essential to determine whether or not new therapies are beneficial and to protect patients from potentially harmful therapeutic interventions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest.

•• Of outstanding interest.

• 1 Hayes MA, Timmins AC , Yau EHS, Palazzo M , Hinds CJ, Watson D : Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*1995 330 1717-1722[MEDLINE Reference]

This prospective randomized **clinical trial** showed that augmentation of oxygen delivery in critically ill patients using dobutamine is potentially harmful.

• 2 McCloskey RV, Straube RC , Sanders C, Smith SM , Smith CR, CHESS **Trial** Study Group: Treatment of **septic shock** with human monoclonal antibody HA-1A: a randomized double-blind, placebo-controlled **trial**. *Ann Intern Med*1994 121 1-5[MEDLINE Reference]

This prospective randomized **clinical trial** showed that HA-1A, a monoclonal antibody directed against the lipid A portion of endotoxin, has no beneficial effect in patients with gram-negative bacteremia and is harmful in patients with sepsis but no gram-negative bacteremia.

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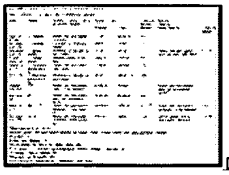
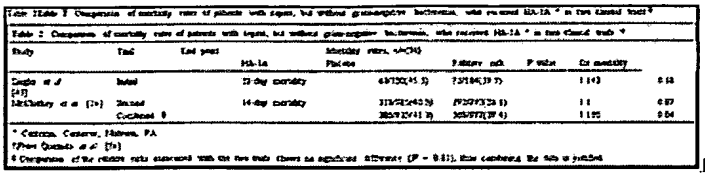
PAF-platelet-activating factor; rhIL-1ra-recombinant human interleukin-1 receptor antagonist; TNF- alpha -tumor necrosis factor- alpha .



[Table 1]



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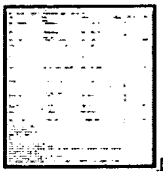

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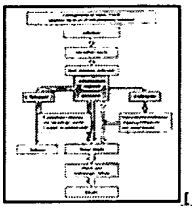

[Figure 1]

Fig. 1. Pathogenesis of **septic shock** stratified by different potential levels of the host's inflammatory response to infection. Some **septic** patients are likely to have an adequate inflammatory response that allows them to adequately control infection and survive. Other **septic** patients may be immunocompromised and have an inadequate inflammatory response that is unable to control infection, resulting in **shock**, multiorgan failure, and death. There are probably other **septic** patients with an excessive inflammatory response that, although needed to control infection, is harmful to the host. Therapeutic strategies may ultimately be tailored to these three different inflammatory responses. Those patients with an adequate response may only need standard therapy with antibiotics and cardiovascular support. Those patients with an inadequate response may need augmentation of some components of the host defense system in addition to standard therapy. Finally, those patients with an excessive response may need anti-inflammatory therapy. To date, the ability to accurately identify these subgroups of patients and to adequately modify therapy is lacking. (Modified from Natanson et al. [7••].)